IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Victor Raso
Prior Application No.: 09/594,366
Prior Application Filing Date: June 15, 2000
Title: IMMUNOLOGICAL CONTROL OF β-AMYLOID LEVELS IN VIVO
Prior Application Art Unit: 1652
Prior Application Examiner: Patterson, C.

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PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Preliminarily, please amend the subject patent application as described below.

In the Claims:

Cancel Claims 1-36 and add new claims 37-67 as shown below.

37. A bispecific antibody comprising:
    a) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and
    b) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope.

38. The bispecific antibody of Claim 37 which is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) and the second hybridoma clone generating the specificity of step b).

39. The bispecific antibody of Claim 37 which is produced by recombinant DNA techniques.

40. The bispecific antibody of Claim 37 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

41. The bispecific antibody of Claim 40 wherein the first and second antibodies are monoclonal antibodies.

42. The bispecific antibody of Claim 40 which is an $F(ab')_2$ hybrid.

43. The bispecific antibody of Claim 39 which is a single chain Fv heterobispecific dimer.

44. The bispecific antibody of Claim 37 wherein the second antibody specificity further confers the ability of the bispecific antibody to inhibit the formation of β-amyloid plaques.

45. The bispecific antibody of Claim 37 wherein the second antibody specificity further confers the ability of the bispecific antibody to disaggregate preformed β-amyloid plaques.

46. The bispecific antibody of Claim 37 wherein the second antibody specificity is further characterized by the ability to hydrolytically cleave β-amyloid.

47. A method for inhibiting the formation of β-amyloid plaques in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

48. The method of Claim 47 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

49. The method of Claim 47 wherein the bispecific antibody is produced by recombinant DNA techniques.

50. The method of Claim 47 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

51. The method of Claim 50 wherein the first and second antibodies are monoclonal antibodies.

52. The method of Claim 50 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

53. The method of Claim 49 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

54. A method promoting the disaggregation of a preformed β-amyloid plaque in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope in a preformed β-amyloid plaque thereby promoting the disaggregation of the plaque; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

55. The method of Claim 54 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

56. The method of Claim 54 wherein the bispecific antibody is produced by recombinant DNA techniques.

57. The method of Claim 54 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

58. The method of Claim 57 wherein the first and second antibodies are monoclonal antibodies.

59. The method of Claim 57 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

60. The method of Claim 56 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

61. A method inhibiting the formation of β-amyloid plaques in the brain of a human, the method comprising:

a) providing a bispecific antibody comprising:

i) a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier; and

ii) a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope, the second antibody further conferring the ability to catalyze the cleavage of β-amyloid, thereby inhibiting the formation of β-

amyloid plaques by reducing levels of free β-amyloid available for incorporation; and

b) introducing the bispecific antibody of step a) into the circulatory system of the human at a concentration sufficient to result in transcytosis of the bispecific antibody across the blood brain barrier.

62. The method of Claim 61 wherein the bispecific antibody is produced by fusing a first and a second hybridoma clone, the first hybridoma clone generating the specificity of step a) i) and the second hybridoma clone generating the specificity of step a) ii).

63. The method of Claim 61 wherein the bispecific antibody is produced by recombinant DNA techniques.

64. The method of Claim 61 wherein the first and second antibody binding specificities are provided by chemically linking a first antibody, or fragment thereof, to a second antibody, or fragment thereof.

65. The method of Claim 64 wherein the first and second antibodies are monoclonal antibodies.

66. The method of Claim 64 wherein the bispecific antibody is an $F(ab')_2$ hybrid.

67. The method of Claim 63 wherein the bispecific antibody is a single chain Fv heterobispecific dimer.

In the Specification:

Please insert the attached Sequence Listing after page 60 of the specification, and renumber the Claims pages to begin with 64.

Amend the second paragraph of Page 7 to read:

Figure 8 is a structural comparison between the native β-amyloid peptide and the transition state phenylalanine statine β-amyloid peptide analog. β-amyloid peptides shown correspond to amino acids 10-13 of SEQ ID NO: 3.

Amend the third paragraph of Page 7 to read:

Figure 9 is a structural comparison between the native β-amyloid peptide and the reduced peptide bond transition state β-amyloid peptide analog. β-amyloid peptides shown correspond to amino acids 10-13 of SEQ ID NO: 3.

Amend the fourth paragraph of Page 7 to read:

Figure 10 is a formulaic representation of the native C-terminal region of β-amyloid, and the phosphonamidate transition state analog of the C-terminal region of β-amyloid ($A\beta_{35-43}$). β-amyloid peptides shown correspond to amino acids 1-9 of SEQ ID NO: 4.

Amend the fifth paragraph of Page 7 to read:

Figure 11 indicates the putative transition state for peptide hydrolysis by zinc peptidases, compared to the phosphonate and phosphonamidate mimics. The β-amyloid peptide fragments shown for the transition-state and phosphonamidate analog are HCRHNCHR (SEQ ID NO: 6). The peptide fragment shown for the phosphonate analog is HCRCHR (SEQ ID NO: 7).

Amend the sixth paragraph of Page 7 to read:

Figure 12 is a structural comparison of the native β-amyloid peptide and the transition state phosphonamidate β-amyloid peptide which has the peptide link between Gly 38 and Val 39 replaced with a phosphonamidate bond. The β-amyloid peptide shown corresponds to amino acid 4-7 of SEQ ID NO: 4.

Attachment 1

Amended paragraphs with corrections shown

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In the Abstract of the Disclosure:

Please cancel the present Abstract of the Disclosure in its entirety, and replace with the following:

> Disclosed are bispecific antibodies comprising a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier, and a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope. Also disclosed are methods for inhibiting the formation of β-amyloid plaques in the brain of a human, or promoting the disaggregation of a preformed β-amyloid plaque. Such methods recite the administration of a bispecific antibody.

REMARKS

Submission of Sequence Listing

The attached paper copy of the Sequence Listing has been prepared in accordance with the provisions of 37 CFR 1.825. Instruction for amendment of the Specification to incorporate the Sequence Listing are provided above.

Also transmitted herewith is a copy of the Sequence Listing in computer readable form. As required by 37 CFR 1.821(f) and (g), Applicants' Attorney hereby states that the content of the Sequence Listing in paper form and on the computer readable form of the Sequence Listing are the same, and the submission includes no new matter.

REMARKS

In light of the above amendments, consideration of the subject patent application is respectfully requested. Please charge any deficiency or overpayment to Deposit Account No. 06-0130.

Respectfully submitted,

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Date: 11/6/01

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